




A *PGC1 β* genetic variant associated with nevus count and melanoma mortality

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Dear Editor,

Proteins of the peroxisome proliferator-activated receptor γ coactivator 1 (PGC1) family are transcriptional coactivators well known for regulating mitochondrial biogenesis and other metabolic functions in multiple tissues ¹. Recently, PGC1 coactivators have also been linked to pigmentation and melanoma skin cancer. In a genome-wide association study ², our group determined the A allele of SNP rs32579 in the *PGC1 β* gene was significantly associated with greater tanning ability, which was successfully replicated in additional samples ³. Furthermore, we demonstrated that the rs32579 A allele was correlated with upregulation of *PGC1 β* gene expression and lower risk of melanoma ³.

However, whether this SNP influences risk of melanoma death remains a question of interest.

We thus investigated the association between the genetic variant rs32579 A and melanoma mortality among 858 melanoma cases. All patients were accrued from a hospital-based case-control study of melanoma skin cancer at The University of Texas MD Anderson Cancer Center (MDACC). Melanoma-specific death was the primary endpoint of the current analysis. We calculated survival time from the date of diagnosis to the date of death from melanoma or the date of the last follow-up, whichever came first. Multivariate Cox proportional hazards regression models, adjusted for age, sex, tumor stage, Breslow thickness, tumor cell mitotic rate, and top two principal components of genetic variance, were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between rs32579 and melanoma mortality. Our result showed that A allele was associated with a lower risk of melanoma disease-specific death (**Table 1**, HR=0.64, 95% CI=0.45-0.91,

p-value=0.013). Previously, the telomere-mitochondrion connection was shown to be regulated by PGC1s⁴, and telomere length was positively correlated with nevus count⁵. We therefore further examined the possible association between this variant and nevus count, a well-known risk factor for malignant melanoma. Among 15,952 individuals of European Ancestry in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), the number of nevi decreases by 0.06 per each A allele (p-value=0.018). Detailed methods of this additional analysis on nevus count have been described previously⁶. Information on study population, genotyping procedure, quality control and imputation are provided in *Supplementary Materials*, for the MDACC study, the NHS and the HPFS.

PGC1 β and PGC1 α normally co-express with each other, and they share a large degree of sequence homology and functional overlap¹. PGC1 α -positive melanomas have been found to have higher rates of survival under oxidative stress compared to PGC1 α -negative melanoma⁷. Last year, Luo *et al.* reported that PGC1 α suppressed melanoma metastasis through direct regulation of parallel-acting transcriptional programs⁸. Though not on PGC1 β , these findings may support our observations in the current population study.

In summary, we so far have shown that this SNP was associated with tanning ability, nevus count, and both melanoma risk and mortality, which further emphasizes the critical role of PGC1s in multiple steps of melanocyte formation and melanoma development. BRAF inhibition regulates PGC1 α expression in BRAF-mutated melanoma, which affects the therapeutic efficacy of BRAF inhibitors⁹. Future studies are warranted to investigate the effect modification of this *PGC1 β* variant on BRAF inhibitors in melanoma treatment.

Table 1. Association between *PGC1 β* rs32579 [#] and melanoma-specific death

Genotype	No. of patients	No. of deaths	HR (95% CI) *	P-value
GG	454	56	1.00 (Ref)	
GA	331	34	0.62 (0.40-0.97)	
AA	73	5	0.44 (0.17-1.10)	
Additive model (G – ref allele, A – test allele)			0.64 (0.45-0.91)	0.013

[#] SNP rs32579 is located on chromosome 5 with BP position at 149210848. The G allele is the major allele, and the A allele is the minor allele. Minor allele frequency = 0.28.

* Cox proportional hazards regression model, adjusted for age, sex, tumor stage, Breslow thickness, tumor cell mitotic rate, and the top two principal components.

Acknowledgements

We are indebted to the participants in the melanoma case-control study at The University of Texas MDACC. We also would like to thank the participants and staff of the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The MDACC study was supported by the National Institutes of Health, National Cancer Institute R01 grant CA100264, the National Cancer Institute SPORE grant P50 CA093459, and the Marit Peterson Fund for Melanoma Research. The studies using the NHS and HPFS data were supported by NIH R01 CA49449, P01 CA87969, UM1 CA186107, UM1 CA167552, and P30 CA008748. The authors assume full responsibility for analyses and interpretation of these data.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Handschin C, Spiegelman BM. Peroxisome proliferator-activated receptor γ coactivator 1 coactivators, energy homeostasis, and metabolism. *Endocrine reviews* 2006;27:728-35.
2. Nan H, Kraft P, Qureshi AA, Guo Q, Chen C, Hankinson SE, Hu FB, Thomas G, Hoover RN, Chanock S. Genome-wide association study of tanning phenotype in a population of European ancestry. *Journal of Investigative Dermatology* 2009;129:2250-7.
3. Shoag J, Haq R, Zhang M, Liu L, Rowe GC, Jiang A, Koulis N, Farrel C, Amos CI, Wei Q. PGC-1 coactivators regulate MITF and the tanning response. *Molecular cell* 2013;49:145-57.
4. Sahin E, DePinho RA. Axis of ageing: telomeres, p53 and mitochondria. *Nature reviews Molecular cell biology* 2012;13:397-404.
5. Han J, Qureshi AA, Prescott J, Guo Q, Ye L, Hunter DJ, De Vivo I. A prospective study of telomere length and the risk of skin cancer. *Journal of Investigative Dermatology* 2009;129:415-21.
6. Li X, Liang G, Du M, De Vivo I, Nan H. No association between telomere length-related loci and number of cutaneous nevi. *Oncotarget* 2016.
7. Vazquez F, Lim J-H, Chim H, Bhalla K, Girnun G, Pierce K, Clish CB, Granter SR, Widlund HR, Spiegelman BM. PGC1 α expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. *Cancer cell* 2013;23:287-301.
8. Luo C, Lim J-H, Lee Y, Granter SR, Thomas A, Vazquez F, Widlund HR, Puigserver P. A PGC1 α -mediated transcriptional axis suppresses melanoma metastasis. *Nature* 2016:422-6.
9. Haq R, Shoag J, Andreu-Perez P, Yokoyama S, Edelman H, Rowe GC, Frederick DT, Hurley AD, Nellore A, Kung AL. Oncogenic BRAF regulates oxidative metabolism via PGC1 α and MITF. *Cancer cell* 2013;23:302-15.